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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/660,384	09/11/2003	Yann Echelard	G0744.70062US01	6941

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EXAMINER	
CROUCH, DEBORAH	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/660,384	ECHELARD ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92-104,106-109,111,112,114,115 and 117-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92-104. 106-109, 111, 112, 114, 115 and 117-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's arguments filed April 23, 2007 have been fully considered but they are not persuasive. The amendment has been entered. Claims 92-104, 106-109, 111, 112, 114, 115 and 117-130 are pending.

The examiner assigned to this application has changed. Deborah Crouch, Ph.D. is now the examiner.

The objection made in the office action mailed October 20, 2006 to claims 92 and 104 is withdrawn because of amendments to the claims.

The rejections made under 35 U.S.C. § 103 in the office action mailed October 20, 2006 has been withdrawn in view of applicant's arguments.

The claims contain format errors. Claim 92 contains two occurrences of "and" at line 13 and 16. Claim 104 also contains a misplaced "and" at line 9, and no "and" before the last method step. Claim 92, line 14 states "one one cell." This appears to a duplicate word. "Said differentiated somatic cell" in claim 104, line 8 and "said differentiated somatic cells" in claim 104, lines 1-11, both lack antecedent basis. Applicant is requested to review the claims for further errors.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 92-104, 106-109, 111, 112, 114, 115 and 117-130 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of a transgenic nonprimate mammal comprising transfecting a first nonprimate mammalian fibroblast cell or cell line with a transgene construct containing a first DNA sequence, selecting a transfected fibroblast into which said first DNA sequence operably linked to a promoter has been inserted into the genome of said first nonprimate

mammalian fibroblast cell or cell line, performing a first nuclear transfer procedure of the same species as the fibroblast to generate a first transgenic nonprimate mammal at least heterozygous for said first DNA sequence, performing a biopsy or other cell selection technique to obtain cells to establish a second nonprimate differentiated somatic cell or cell line from said first transgenic nonprimate mammal, characterizing said second nonprimate mammalian cell or cell line using molecular biology methods to ensure that the second nonprimate mammalian differentiated somatic cell or cell line is at lest heterozygous for said first DNA sequence, performing a second nuclear transfer procedure of the same species as the fibroblast with at least one cell of said second nonprimate mammalian differentiated somatic cell or cell one to produce at least a second nonprimate mammal at least heterozygous for said first DNA sequence, and producing the second transgenic nonprimate mammal or a method of preparing a genetically engineered transgenic mammal comprising inseminating a first female nonprimate mammal recipient with semen from a transgenic nonhuman primate of the same species known to have a transgene present and expressed, obtaining a transgenic nonprimate mammal embryo from said first female recipient, obtaining a somatic cell from said embryo, culturing said differentiated somatic cell in a suitable medium, such that a different somatic cell line is obtained, performing a nuclear transfer procedure of the same species as the donor cell with said differentiated somatic cell to produce at least one transgenic nonprimate mammal at heterozygous for said transgene, wherein said transgenic encodes a desired gene operably lined to a tissue specific promoter; and producing the transgenic nonprimate mammal, does not reasonably provide enablement for the breadth of the claims as presently written. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At the time of filing, the art taught unpredictable results in the cloning of primates. The cloning of monkeys had only been successful using embryonic cells (Mitalipov, abstract). Mitalipov further states, clearly, that somatic differentiated cell cloning, as is part of the present methods, has not been accomplished in primates (Mitalipov, page 1367, col. 2, parag, 3, lines 1-3). Simerly, states that in rhesus monkey NT units, DNA and microtubule imaging showed disarrayed mitotic spindles with misaligned chromosomes, which resulted in unequal chromosome segregation and aneuploid embryos (Simerly, page 297, col. 2, parag. 1, lines 5-11). Further, the claims encompass cross-species nuclear transfer that is when the donor cell and oocyte are of different species. This was regarded by the art as lacking enablement at the time of filing. Meirelles demonstrates that methods of nuclear transfer where the nuclear material of *Bos indicus* is inserted into the oocyte of *Bos taurus* produces calves comprising the nuclear material of *Bos indicus* and the mitochondria of *Bos taurus*. Meirelles *et al.* teach that previous attempts to use the *Bos* oocyte as hosts for nuclear transfer from unrelated species allowed development to the blastocyst stage, and conclude that incompatibility among the nuclear and mitochondrial genetic systems is responsible for the early arrest. Meirelles also points to similar failures using *Mus caroli* and *Mus musculus* citing Dominko. Meirelles conclude stat in light of their results and the failures of the prior art, that nuclear transfer across subspecies barriers is possible. (see Meirelles, pp. 351-355). In addition, the claims encompass methods of nuclear transfer when the oocyte is off a different species than the surrogate mother animal. Further, in the production of sheep goat chimeras, there were biases towards chimeras whose genotype and phenotype was most like that of the recipient, and that the successful production of chimeras resided in the neutralization of incompatibility between the chimeric embryo (Fehilly et al (1985), page 221, parag. 1). Thus the claims are not enabled as broadly claimed.

The issue surrounding transfection of cells, either to express a DNA sequence encoding a protein of interest or knocking out a gene of interest, is selection of the transfected cells. Nuclear transfer requires the donor nucleus be diploid. An aneuploid or polyploidy donor cell will not permit development of the cloned nonprimate mammal. In addition, Clark teaches that about 45-population doubling are required to generate targeted cells (Clark, page 268, col. 2, parag. 1, lines 1-5). Denning teaches primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence (Denning, page 222, col. 1, lines 5-8). In a study of sheep and goat primary somatic cells, Denning found that of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. Further, a comparison of separate Black Welsh sheep primary cell fibroblast cultures showed vast differences in the number of doublings prior to senescence; 110 doublings versus 40 doublings (Denning, page 224, col. 2, lines 16-19). In a similar analysis of pig primary cultures, fibroblasts, as in the sheep study, became the predominant cell-type after three passages, but, unlike sheep, pig fibroblasts underwent a crisis after 40 population doublings and had an unstable karyotype (Denning, page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). Although experimentation is required for obtaining a fibroblast culture capable of sufficient selection prior to senescence, for the breath of any differentiated somatic cell, the degree of experimentation becomes unpredictable.

Claims 112 and 118 are not enabled for nuclear transfer when a neural cell is the nuclear donor. At the time of filing, the art taught mice could not be produced by nuclear transfer using a neural cell as nuclear donor for unknown reasons (Wakayama, page 373, col. 1, parag. 1, lines 1-2).

Further claims 92-103, 106-108, 111, 112, 119 and 126-130 lack an enabled use because a DNA sequence encoding a protein would necessarily require operable linkage to a promoter or expression regulatory sequences.

Thus, at the time of filing the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 92 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 92 states "molecular biology methods." The metes and bounds of the term are not clear. If the presence of the DNA sequence is determined by antibody binding, is this a molecular biology method, or are only methods of analyzing the DNA sequence directly or its mRNA product encompassed? Applicant may wish to delete the term.

The claims are free of the prior art. At the time of filing, the prior art did not teach or suggest methods of recloning where donor cells were selected and analyzed for at least the presence of a transgene. The closest prior art U.S. Patent 6,252,133 (parag. 54) and U.S. Patent 6,011,197 (parag. 142).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 6:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

July 2, 2007